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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,956	10/10/2001	Xuehai Ye	64688/152	6226

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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	7

DATE MAILED: 05/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,956	YE ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-7 are pending in the application.

The substitute specification submitted in paper No. 5 (filed 12/26/01) has been entered.

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Specifically, the declaration was amended by the insertion of the word "provisional" before the word patent. However, the alteration was made without initialing or dating the alteration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase, "an effective amount of adenoviral vector". This phrase renders the claim indefinite because it is unclear what constitutes "an effective amount". There is no definition of "effective amount" in the specification. Without a clear definition of "effective amount" the metes and bounds of the claim cannot be determined. Adenoviral vectors

are well known in the art as vectors useful in gene therapy. Therefore, "an effective amount" could be interpreted as an amount that results in amelioration of the symptoms of a disease or disorder. However, "an effective amount" could also be interpreted to mean an amount that results in viral infection of the target cells. Claim 1 also recites the phrases "at an effectively slow rate" and "over an effective period of time". These phrases also render the claim unclear because "an effectively slow rate" and "an effective period of time" are not defined in the specification, therefore the metes and bounds of the claim cannot be determined and the claim is indefinite. Claims 2-7 depend on claim 1 and are rejected for the same reasons.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 2 is drawn to an adenoviral viral vector comprising a control element that preferentially express a gene of interest in renal glomerular cells. Therefore, the claim encompasses promoter elements for which no written description is provided in the specification. This genus of elements is not represented in the specification by even a single example. Thus, applicant has not expressed possession of *any* such promoter element. The written description guidelines note "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common

attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, the function of the promoter elements is disclosed (preferential expression in renal glomerular cells), but no structural limitations or requirements are provided for guidance on the identification of promoter elements which meet these functional limitations.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, no promoter elements are described.

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of *any* promoter element which have the claimed function (preferential expression in renal glomerular cells). Furthermore, it is noted that at the time of invention, there was not a single renal glomerular cell specific promoter known in the art, as evidenced by Wong et al. (Am. J. Physiol. Renal Physiol., Vol. 279:F1027-F1032, December 2000) which identifies a glomerular-specific promoter from the human nephrin gene (see first sentence of abstract) states, "this represents the first glomerular-specific promoter to be identified." (See abstract).

Therefore, the claims fail to meet the written description requirement by encompassing promoter elements which are not described in the specification.

5. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As mentioned above, the claims are unclear and open to multiple interpretations based on the interpretation of the phrase "an effective amount". Interpretation of "an effective amount" as an amount that ameliorates the symptoms of a disease or disorder warrants the rejection under 35 U.S.C. 112, first paragraph that follows.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

As mentioned above, the instant claims can be interpreted to mean delivering the adenoviral vector in an amount effective to treat a disease or disorder. This interpretation of the claim encompasses gene therapy.

The breadth of the claims

The breadth of the claims is very broad. For instance, the claims delivering an adenoviral vector encoding a gene of interest to the kidney glomerular cells of a mammalian subject. The subject can be any species of mammal, including rats and humans. Furthermore, the claims encompass treating any disorder associated with the kidney in any species of animal, including humans.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to a target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear", and sites specific examples (see page 409, first col.). Crystal also teaches, "Among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity, and to enable the transferred gene to be regulated" (see p. 409, second column). Verma et al. (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects). More recently, Walther and Stein (2000) indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section). Crystal also teaches that "humans are not simply

large mice" and that predictions from gene transfer studies in animals has not been borne out in human safety and efficacy trials (see p. 409, first column).

Working Examples and Guidance in the Specification

The specification has no working examples, whatsoever, of kidney disease/disorder treatment using an adenoviral vector. The specification, does providing examples demonstrating that the method can be used to deliver an adenoviral vector comprising a gene of interest to the glomerular cells of a rat kidney *in vivo*, and demonstrates that the gene of interest (lacZ) can be expressed in the glomerular cells. Therefore the examples address one aspect of unpredictability recognized in the art, namely the problem of specific delivery of the vector. However, the examples do not address any of the other art-recognized obstacles mentioned above. For instance, there are no examples or guidance that the vector can effectively express a therapeutic gene of interest, that the therapeutic gene could be properly expressed for the required duration of time and at an appropriate level to be effective. The working examples also do not show that the administration is functional in human subject *in vivo*. The examples are only in rats *in vivo*, and in human cells *in vitro*. As mentioned above, results in animals cannot be reliably extrapolated to humans.

Also the specification does not offer any guidance on which kidney diseases would be responsive to the treatment, or even which genes of interest would be effective at treating *any* kidney disease.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of the efficacy of the adenoviral system would first require that a gene of interest could be effective at treating a kidney disease in vitro. The adenoviral vector comprising the therapeutic gene would then have to be delivered to animal models of the disease to determine efficacy in animals. Followed by clinical trials in humans. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, and 3-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Sukhatme (U.S. Patent 5,869,230).

As mentioned above, the claims are unclear and open to multiple interpretations based on the interpretation of the phrase "an effective amount". Interpretation of "an effective amount" as an amount allows for infectivity of the kidney cells warrants the rejection under 35 U.S.C. 102(b), that follows.

Sukhatme teaches a method of infecting glomerular cells of a kidney of a mammalian subject (here, a rat—see col. 16, lines 1-28), with a recombinant adenoviral vector carrying a gene of interest (here, lacZ—see col. 15 lines 1-45), comprising the step of infusing intra-renal arterially in a single pass through the renal artery an effective amount into said kidney at an effectively slow rate over an effective slow time under conditions that glomerular cells are infected with said vector (see col. 17, lines 60-63).;

Wherein the kidney is maintained at a reduced temperature during the infusion procedure (see col. 10, lines 51-54);

Wherein the aorta is clamped above and below the superior mesenteric renal artery of the kidney (see col. 9, lines 10-15);

Wherein the infusion is between 15 and 120 minutes (here, 45 minutes—see col. 16, lines 25-26).

Although Sukhatme does not explicitly teach that the infusion is through the superior mesenteric renal artery, that the renal artery is cannulated directly without clamping of the aorta, that the infusion rate is $0.1\text{-}0.5\text{x}10^{11}$ particles per minute, or that the renal vein is concurrently

cannulated. However, it is only a matter of routine optimization of Sukhatme to make these modifications, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Therefore, routine optimization is not considered inventive.

In the instant case, Sukhatme teaches the general conditions of delivering an adenoviral vectors to kidney cells, including renal glomerular cells, by injecting the virus into a renal-associated artery. Although Sukhatme teaches that only 1-2% of glomerular cells are infected (see col. 17, lines 61-63), it is only a matter of routine experimentation to alter the point of injection (it is noted that vectors injected into the superior mesenteric artery would travel through the renal artery to reach the kidney), the infusion rate, and the clamping or non-clamping and of kidney-associated blood vessels in order to optimize the delivery of the adenoviral to renal glomerular cells. It is noted that cannulation of the renal vein does not effect the delivery of the vector to the renal cells, but rather is a means of collecting non-infused vectors in order to reduce the risk of infecting non-kidney cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
May 17, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER